PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 67789-1435	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/US2004/030607	International filing date *(day/month/year)* 17 September 2004 (17.09.2004)	Priority date *(day/month/year)* 06 October 2003 (06.10.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant CEDARS-SINAI MEDICAL CENTER		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 19 September 2006 (19.09.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Beate Giffo-Schmitt e-mail: pt03@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	21 JUL 2006
Applicant's or agent's file reference 081476-0311690	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US04/30607	17 September 2004 (17.09.2004)	06 October 2003 (06.10.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC: **G01N 33/567**(2006.01)
USPC: 435/7.21

Applicant

CEDARS-SINAL MEDICAL CENTER

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☒ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	16 June 2006 (16.06.2006)	Christina Borgeest Telephone No. 571-272-1600

Form PCT/ISA/237 (cover sheet) (April 2005)

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/30607

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US04/30607

Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	2-17,19-33 and 37	YES
	Claims	1, 18, 34, 35, 36, 38	NO
Inventive step (IS)	Claims	13-17, 32	YES
	Claims	1-12, 18-31, 33-38	NO
Industrial applicability (IA)	Claims	1-38	YES
	Claims	NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/US04/30607

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

Claim 30 is objected to as lacking clarity under PCT Rule 66.2(a)(v) because of the claim is not fully supported by the description. The description does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art because: the description does not give support for all of the diseases recited in claim 30.

Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:

1. Claims 1, 18, 34, 35, 36, 38 lack novelty under PCT Article 33(2) as being anticipated by Spencer et al. (Bone Marrow Transplant. 2001; 28: 1019-22). Spencer et al. teach human stem cells expressing CXCR4 and treatment of a disease condition using said cells, and since SDF-1 is the receptor for CXCR4 (as evidenced by Möhle et al., Ann N Y Acad Sci. 2001 938: 26-34; discussion 34-35-see p. 27, 1st paragraph), this meets the claim limitations of claim 1.

2. Claims 1-4, 18-22 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the immediately preceding paragraph and further in view of Hugnot et al. (Develompental Neuroscience. 2001: 12: 2237-2241) and Murphy et al. (Prog Neurobiol. 1997; 52: 355-78). Spencer et al. do not specifically teach stem cells exhibiting A2B5 and GFAP astrocytic precursor markers. Hugnot et al. teach that embryonic hippocampal cells from the MHP36 neural multipotent cell line that develop markers (GFAP) when cultured with LIF and (A2B5) at low cell density. Murphy et al. teach that LIF receptor null mutant mice have drastically reduced number of astrocytes (p. 372, left column, 4th paragraph), thus suggesting the importance of LIF signaling in the brain. Furthermore, stem cells implanted in vivo (into the brain) would by necessity have low cell density compared with in vitro culture conditions. Thus it is inherently obvious that a portion of stem cells implanted into the brain would develop into astrocytic precursor cells because the prior art

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In case the space in any of the preceding boxes is not sufficient.

teachings suggest that the conditions in vivo would be right for this to occur.

3. Claims 1, 5-9, 12, 37 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the 1st paragraph and further in view of Ehtesham et al. (Cancer Res. 2002; 62: 5657-63. As stated in the 1st paragraph, Spencer et al. teach human stem cells expressing CXCR4, but they do not teach the stem cell comprising IL-12. Ehtesham et al. teach IL-12 producing neural stem cells (see for example, abstract; p. 5657, under Materials and Methods). It would have been obvious to modify the teachings of Spencer et al. by developing IL-12 producing stem cells because according to Ehtesham et al., the tumoricidal potency of IL-12 combined with the tumor tracking capability of NSC may offer an effective treatment for glioma (see p. 5663, left column, 2nd paragraph). One could expect success because the teachings of Ehtesham et al. suggest promise for a new treatment of glioma.

4. Claims 1, 8, 10 and 12, 37 lacks an inventive step under PCT Article 33(3) as being obvious over the prior art as applied to the 1st paragraph and further in view of Benedetti et al., Nat Med. 2000; 6: 447-50. As stated in the 1st paragraph, Spencer et al. teach human stem cells expressing CXCR4, but they do not teach the stem cell comprising Il-4. Benedetti et al. teach IL-4 producing neural stem cells (see abstract; p. 449, under Methods). It would have been obvious to modify the teachings of Spencer et al. by developing IL-4 producing stem cells because according to Benedetti et al., neural progenitor cells engineered to release IL-4 can have a strong anti-tumor effect and is safer than retrovirus-mediated, in vivo transfer of IL-4 (see p. 448, right column, 2nd paragraph).

5. Claims 1, 8, 11 and 12, 37 lack an inventive step under PCT Article 33(3) as being obvious over the prior art as applied in the 1st paragraph and further in view of Ehtesham et al. (Cancer Res. 2002; 62: 7170-4). As stated in the 1st paragraph, Spencer et al. teach human stem cells expressing CXCR4, but they do not teach the stem cell comprising TRAIL. Ehtesham et al. teach TRAIL producing neural stem cells (see abstract; p. 7170, Materials and Methods). It would have been obvious to modify the teachings of Spencer et al. by developing TRAIL producing stem cells because according to Ehtesham et al., neural stem cells containing TRAIL was effective at killing glioma cells but not toxic to normal tissue, thus is a promising therapy (see p. 7174, left column, 2nd paragraph).

6. Claims 18-27, 30, 31, 33 lack an inventive step under PCT Article 33(3) as being obvious over Ehtesham (cited in 3rd paragraph) in view of Spencer et al. (cited above), Hugnot et al. (cited above) and Murphy et al. (cited above). Ehtesham et al. teach a method of administering neural stem cells expressing IL-12 (see p. 5657, Materials and Methods, under Inoculation of Established Intracranial Gliomas with NSC). Ehtesham do not teach that the stem cells express CXCR4, or that they are astrocytic progenitor cells exhibiting A2B5 or GFAP. The combined teachings of Hugnot, Murphy and Ehtesham and colleagues teach that embryonic hippocampal cells from the MHP36 neural multipotent cell line develop markers astrocytic markers (GFAP) when cultured with LIF and (A2B5) at low cell density and because LIF signaling is important in the brain and stem cells implanted in vivo (into the brain) would by necessity have

Supplemental Box
In case **the space in any of the preceding boxes is not sufficient.**

low cell density compared with in vitro culture conditions, it would be inherently obvious that a portion of stem cells implanted into the brain would develop into astrocytic precursor cells because the prior art teachings suggest that the conditions in vivo would be right for this to occur.

7. Claims 18-26, 28, 30, 31, 33 lack an inventive step under PCT Article 33(3) as being obvious over Benedetti et al. (cited in 4th paragraph) in view of Spencer et al. (cited above), Hugnot et al. (cited above) and Murphy et al. (cited above). Benedetti et al. teach a method of administering IL-4 producing neural stem cells (see abstract; p. 450, under In vivo experiments). Benedetti et al. do not teach that the stem cells express CXCR4, or that they are astrocytic progenitor cells exhibiting A2B5 or GFAP. The combined teachings of Hugnot, Murphy and Ehtesham and colleagues teach that embryonic hippocampal cells from the MHP36 neural multipotent cell line develop markers astrocytic markers (GFAP) when cultured with LIF and (A2B5) at low cell density and because LIF signaling is important in the brain and stem cells implanted in vivo (into the brain) would by necessity have low cell density compared with in vitro culture conditions, it would be inherently obvious that a portion of stem cells implanted into the brain would develop into astrocytic precursor cells because the prior art teachings suggest that the conditions in vivo would be right for this to occur.

8. Claims 18-26, 29, 30, 31, 33 lack an inventive step under PCT Article 33(3) as being obvious over Ehtesham et al. (cited in 5th paragraph) in view of Spencer et al. (cited above), Hugnot et al. (cited above) and Murphy et al. (cited above). Ehtesham et al. teach a method of administering TRAIL producing neural stem cells (see abstract; p. 7170, Materials and Methods). Ehtesham et al. do not teach that the stem cells express CXCR4, or that they are astrocytic progenitor cells exhibiting A2B5 or GFAP. The combined teachings of Hugnot, Murphy and Ehtesham and colleagues teach that embryonic hippocampal cells from the MHP36 neural multipotent cell line develop markers astrocytic markers (GFAP) when cultured with LIF and (A2B5) at low cell density and because LIF signaling is important in the brain and stem cells implanted in vivo (into the brain) would by necessity have low cell density compared with in vitro culture conditions, it would be inherently obvious that a portion of stem cells implanted into the brain would develop into astrocytic precursor cells because the prior art teachings suggest that the conditions in vivo would be right for this to occur.

9. Claims 13-17, 32 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest a method of assessing the tumor tropic potential of a neural stem cells by determining the expression level of CXCR4, wherein the neural stem cells are positive for A2B5 and GFAP, nor does it teach a method of coadministering stem cells expressing CXCR4 with a volume of SDF-1 with the neural stem cells.

10. Claims 1-38 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.